PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of Letant et al. Application No.: 10/677,395 Filed: 10/01/2003 For: FUNCTIONALIZED APERTURES FOR THE DETECTION OF CHEMICAL AND BIOLOGICAL MATERIALS	Group Art Unit: 1634 Examiner: CROW, Robert T. Attorney Docket No.: LLNLP010/IL-11138 Date: February 19, 2009

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: Board of Patent Appeals and Interferences

REPLY BRIEF (37 C.F.R. § 1.193)

This Reply Brief is being filed within two (2) months of the mailing of the Examiner's Answer on Dec. 23, 2008.

Following is an issue-by-issue reply to the Examiner's Answer.

In section (10) "Response to Argument" of the Examiner's Answer mailed Dec. 23, 2008, the Examiner has broken Appellants' arguments down into four main arguments, and presented a response to each generalized argument. Accordingly, the following reply will address each of the four Examiner responses.

Response to summarized argument 1:

Issue # 1:

The Examiner first argues on p. 15 of the Examiner's Answer mailed Dec. 23, 2008 (hereinafter "Examiner's Answer") that Branton specifically teaches the crosslinking of the polymerase to the aperture forms a protein solid-state complex, and thus Branton indicates that DNA polymerase is a protein. Because Branton does not overtly disclose any functional groups, to meet this limitation, the Answer again goes on to assert that polymerases are proteins, which comprise chemical functional groups as evidenced by Stryer. Thus, asserts the Examiner, on p. 17 of the Examiner's Answer, DNA polymerase I inherently comprises functional groups because DNA polymerase I is unequivocally a polypeptide made of amino acids having side chains comprising functional groups.

Appellants again respectfully challenge this assertion. Appellants hereby incorporate by reference the arguments made in the Appeal Brief.

In addition, Appellants again argue that there has been no showing that DNA polymerase I includes functional groups. The Examiner's logic is that DNA polymerase I is a polypeptide made of amino acids having side chains comprising functional groups. However, referring to p. 14 of Stryer, several of Stryer's amino acids do not contain functional groups even in their amino acid state. See, e.g., Stryer Fig. 2-8, glycine, alanine. There has been no showing that DNA polymerase I is not based on one of these amino acids. Thus, the rejection is not properly supported.

Moreover, as asserted by Appellants in the Appeal Brief, the rejection improperly relies on a long chain of possibilities. Again, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). Rather, to establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted, emphasis added). In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

Appellants again respectfully assert that the Examiner's assertion of inherency improperly relies on possibilities and probabilities, in violation of *In re Robertson, supra*. First, the Examiner has not shown that all amino acids have functional groups. In fact, it has been shown above that not all amino acids have functional groups. Thus we have a first possibility, that the polymerase relied upon is made up of amino acids that do not have functional groups. Again, no showing has been made of which amino acids are bases for DNA polymerase I.

Then consider that proteins are *reaction products* of amino acids. In other words, the base amino acid, which may or may not have a functional group, is then reacted with something to form a protein. Does a functional group of the amino acid retain its functionality, if it even has one? In other words, is the functional group still a functional group, or, now that the amino acid has reacted, is the functional group merely a nonfunctional branch of the protein, or even coupled to the other reactant? Possibly. From the evidence of record, we do not know. As should now be apparent, the logic of the rejection relies on too many levels of possibilities to support the Examiner's assertion of inherency. Again, "[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson, supra.*

Moreover, Stryer does indicate that DNA polymerase 1 is an enzyme, but it is known that not all enzymes are proteins. Therefore, the rejection relies on the *possibility* that Branton's polymerase is not only the same as that in Stryer, *and also* that Stryer's DNA polymerase is a protein, *and yet further* that the protein is formed of amino acids that might have functional groups, *and even further that*, after all the processing necessary to convert the amino acids to the DNA polymerase, what might have been functional groups (if present) in the starting material are still functional groups rather than nonfunctional. As can be seen, the logic of the rejection relies on too many levels of possibilities to support the Examiner's assertion of inherency. Again, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert, supra*. Rather, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson, supra.*

Nor can we simply take the Examiner's word for it. Again, to establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *In re Robertson, supra.*

Additionally, the Examiner asserts on p. 17 of the Examiner's Answer that the peptide bond is an amide bond, and an amide is a chemical functional group. This assertion relies on official notice, as no evidence has been presented to show that the peptide bond in DNA polymerase I is functional. However, official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known. As noted by the court in *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970), the notice of facts beyond the record which may be taken by the examiner must be "capable of such instant and unquestionable demonstration as to defy dispute" (citing *In re Knapp Monarch Co.*, 296 F.2d 230, 132 USPQ 6 (CCPA 1961)). It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697. Appellants respectfully challenge the taking of official notice, and respectfully assert that it is not well-known, or common knowledge in the art that is capable of instant and unquestionable demonstration as being well-known, that the amide bond in DNA polymerase I is functional. Accordingly, absent some evidence on the record, the Examiner's assertion is improper.

For any of the foregoing reasons, the rejection of claims 7-8 and 16-18 is improper.

Issue # 2:

In the Examiner's Answer, the Examiner again asserts that Branton teaches a substrate but does not teach or suggest a macrocyclic ring. Thus, the rejection relies on Hoger to disclose a macrocyclic ring.

Appellants respectfully traverse the rejection as failing the *Graham* test. Specifically, the combination proposed in the rejection fails at least the first element of the *Graham* test for the reasons set forth in the Appeal Brief, which has been incorporated by reference, and which are set forth below.

First, the Examiner has failed to provide a reasonable motivation to make the proposed combination of features based on knowledge generally available to those skilled in the art and not provided by Applicants in the present disclosure.

> "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd.Pat.App.&Inter.1985).

Here, the Examiner has indicated that the motivation to combine the references is based on creating an apparatus having cyclical molecules therein that recognize guest molecules with precise complimentarity as taught by Hoger. However, as pointed out in detail below, neither reference teaches or suggests a macro-cyclic ring coupled to a solid substrate, much less at or near the circumference at one of the cylindrical portion of said at least one aperture, as claimed. Moreover, as discussed in detail below, one cannot simply combine random chemical structures and expect to have predictable results. Rather, as well known to those skilled in the chemical arts, one cannot accurately predict what the result of combining chemical structures will be, much less how the combination will perform, absent some teaching from one who has made and studied the combination.

Thus, the only conclusion that can be drawn is that the combination of features proposed in the rejection has been impermissibly drawn from Appellants' disclosure. Again, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure *In re Vaeck, supra.*

Next, the claimed invention would <u>not</u> have been predictable from the bare teachings of the prior art itself, or in knowledge generally known to those skilled in the art. The United States Supreme Court has acknowledged that there is no obviousness where the end result is unpredictable. In the recent case, *KSR International v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), the Court's analysis included by implication the traditional notion that evidence of unpredictable results is evidence of non-obviousness. Therefore, even though the Court made sweeping changes to the obviousness analysis, it acknowledged that if the result of the proposed modification or combination of features is unpredictable, there is no obviousness.

The courts have repeatedly stated that the chemical arts are, by their very nature, unpredictable. This case is no different. In the instant rejection, the Examiner proposes replacing Branton's polymerase with a cyclic molecule from Hoger. However, no showing has been made that such a substitution would work, and allow Branton's device to continue to operate. Rather, any result of such a substitution is truly unpredictable. For instance, will Branton's crosslinkers couple to Hoger's cyclical molecule? If so, what will the effect be on the resultant diameter of the cyclical molecule? Will it still allow passage of Branton's single strand of DNA? Further, would Branton's invention even work after such a substitution? (Note Branton's reliance on the "biological motor" created by polymerase and DNA at p. 36, line 23 to p. 38, line 30.)

The lack of any description of using cyclicals in Branton is further evidence that such a substitution was not predictable to those skilled in the art.

Moreover, the Examiner cites Scheme 4 on p. 2689 of Hoger for the proposition that the rings can be coupled to a support. However, as clearly shown on p. 2689 of Hoger and described in the first partial paragraph of col. 1 thereof, Scheme 4 is a synthesis process in which the precursors are attached to the solid support and, upon formation of the ring break free. Assuming the same result in Branton if Hoger's rings were employed therewith, the rings would appear to break free from Branton's aperture.

Further, a reading of the column on p. 2689 of Hoger directly under the drawing labeled "Scheme 4" indicates that the precursors coupled to the solid substrate are found to couple together, voiding the reaction that is to create the ring. Accordingly, whether one of Hoger's rings would form in Branton's aperture, or would couple with another of the precursors, adds yet another layer of unpredictability to the combination proposed by the Examiner.

Moreover, the Examiner has provided no showing of how such a ring could be coupled to Branton's aperture.

Because the result of the substitution proffered in the rejection is unpredictable, the claimed invention is not obvious. Accordingly, the rejection is improper.

In the Advisory Action mailed June 24, 2008, the Examiner notes that the arguments of counsel cannot take the place of evidence on the record. However, the burden does not lie on the Applicant to show the unpredictability of the results, but rather

on the Examiner to show the predictability of the results with a high degree of certainty. In this case, he has not.

Expanding on the points above, even assuming arguendo that substitution of Branton's polymerase with Hoger's cyclic molecule would somehow render predictable results, such results would appear to render Branton's device inoperable, and thus unsatisfactory for its intended purpose.

Appellants therefore respectfully traverse the rejection of claim 1 as being improper, as the proposed modification would render Branton's invention unsatisfactory for its intended purpose. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Particularly, the purpose of Branton's system is to analyze portions of a DNA strand as it moves through a hole. However, no showing has been made that Branton's device would be able to properly analyze DNA without the polymerase. Rather, the Examiner appears to be assuming that Hoger's cyclic molecule will perform the same function as the polymerase. [Appellants note that the Examiner has gone to great lengths to characterize a polymerase in the rejection of claim 7. Now it appears that the Examiner is asserting that the polymerase can be simply swapped with some other molecule.]

Further, if Hoger's cyclical molecule were added as suggested by the Examiner, the DNA strand might couple with the cyclical and stop. If so, Branton's device would no longer be able to analyze the strand in the hole, or any other strand in the sample, as Branton requires pulling the DNA strand through the aperture in sequential order. *See* Branton's Abstract. *See also* section G of the Office Action mailed April 11, 2008, where the Examiner states that Branton's device is "for evaluation a polymer molecule by causing the polymer molecule to move through an aperture in sequential order."

Moreover, the Examiner indicates in section F of the Office Action mailed April 11, 2008 that the Applicant's argument regarding the binding of the Branton's DNA strand to Hoger's cyclical if added to Hoger's aperture undermines Applicant's claim 11 (withdrawn). The Examiner is respectfully directed to claim 11, which recites "wherein said aperture is functionalized to bind to a specific biological or chemical moiety".

Accordingly, Applicant's arguments do not undermine the embodiment of claim 11. Rather, the binding is an intended function of claim 11. In sharp contrast, such binding would indeed undermine Branton's device which, as set forth by the Examiner in section G of the Office Action mailed April 11, 2008, is "for evaluation a polymer molecule by causing the polymer molecule to move through an aperture in sequential order."

For any one of the foregoing reasons, Branton's device would be rendered inoperable, in violation of *In re Gordon, supra.*

Accordingly, the rejection is improper for this reason as well.

Moreover, the rejection based on Hoger is not supported. The rejection, at Section 6, 7th paragraph, relies on Hoger' Scheme 4 to show macro-cyclic rings attached to solid supports. However, a reading of the column on Hoger p. 2689 directly under the drawing labeled "Scheme 4" indicates that Scheme 4 is not preferred. Particularly, the author notes that the precursors are found to couple together, voiding the reaction that is to create the ring. Further, at one point, the author refers to Scheme 4 as requiring "extreme approaches". *See* Hoger, p. 2689, first column.

In the Advisory Action mailed June 24, 2008, the Examiner appears to agree that Hoger Scheme 4 does not support the previous assertion that Hoger teaches macro-cyclic rings attached to solid supports in a manner that would meet the claim limitations. Particularly, the Examiner states in section C that "Applicant's citation is directed specifically to solid state reactions of precursors of macrocyclic ring, nor the preformed ring itself. Thus, Applicant's citation has no bearing on the attachment of a preformed ring onto a solid substrate after formation of the ring." (emphasis added) Appellants agree that Hoger Scheme 4 is directed to synthesis of the rings on a solid support, not to attachment of preformed rings onto a solid surface. Accordingly, because the Examiner admits that Hoger's Scheme 4 is a synthesis reaction that does not relate to attachment of preformed rings to a solid surface, the rejection improperly relies upon Hoger's Scheme 4 to show attachment of a ring to a solid support. (*See* Office Action mailed April 11, 2008, section 6, 7th paragraph.)

In any case, Hoger appears to teach away from coupling rings to a solid support. A *prima facie* case of obviousness may also be rebutted by showing that the art, in any

material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

The rejection, at Section 6, 7th paragraph, relies on Hoger' Scheme 4 to show macro-cyclic rings attached to solid supports. However, a reading of the column on Hoger p. 2689 directly under the drawing labeled "Scheme 4" indicates that Scheme 4 is not preferred. Particularly, the author notes that the precursors are found to couple together, voiding the reaction that is to create the ring. Further, at one point, the author refers to Scheme 4 as requiring "extreme approaches". *See* Hoger, p. 2689, first column.

Accordingly, because Hoger teaches away from a ring coupled to a solid support, the rejection violates the rule of *In re Geisler, supra*, and must be withdrawn.

For any of the foregoing reasons, reconsideration and allowance of claim 1 is respectfully requested.

Claims 2-5 and 12-15 depend from claim 1, and therefore incorporate the limitations of claim 1. By virtue of their dependence, claims 2-5 and 12-15 are also believed to be allowable. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Reconsideration and allowance of claims 2-5 and 12-15 is respectfully requested.

Further, the deficiencies of the reliance on Stryer set forth above are incorporated by reference here for those claims for which the rejection relies on Stryer.

On p. 21 of the Examiner's Answer, the Examiner asserts that *KSR v. Teleflex* eliminates the requirement that a specific teaching, suggestion or motivation is required to support a finding of obviousness. However, this applies only where the result is predictable. In sharp contrast, the claimed invention would not have been predictable from the bare teachings of the prior art itself, or in knowledge generally known to those skilled in the art. The United States Supreme Court has acknowledged that there is no obviousness where the end result is unpredictable. In the recent case, *KSR International v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), the Court's analysis included by implication the traditional notion that evidence of unpredictable results is evidence

of non-obviousness. Therefore, even though the Court made sweeping changes to the obviousness analysis, it acknowledged that if the result of the proposed modification or combination of features is unpredictable, there is no obviousness.

The courts have repeatedly stated that the chemical arts are, by their very nature, unpredictable. This case is no different. In the instant rejection, the Examiner proposes replacing Branton's polymerase with a cyclic molecule from Hoger. However, no showing has been made that such a substitution would work, and allow Branton's device to continue to operate. Rather, any result of such a substitution is truly unpredictable. For instance, will Branton's crosslinkers couple to Hoger's cyclical molecule? If so, what will the effect be on the resultant diameter of the cyclical molecule? Will it still allow passage of Branton's single strand of DNA? Further, would Branton's invention even work after such a substitution? (Note Branton's reliance on the "biological motor" created by polymerase and DNA at p. 36, line 23 to p. 38, line 30.)

The lack of any description of using cyclicals in Branton is further evidence that such a substitution was not predictable to those skilled in the art.

Moreover, the Examiner cites Scheme 4 on p. 2689 of Hoger for the proposition that the rings can be coupled to a support. However, as clearly shown on p. 2689 of Hoger and described in the first partial paragraph of col. 1 thereof, Scheme 4 is a synthesis process in which the precursors are attached to the solid support and, upon formation of the ring break free. Assuming the same result in Branton if Hoger's rings were employed therewith, the rings would appear to break free from Branton's aperture.

Further, a reading of the column on p. 2689 of Hoger directly under the drawing labeled "Scheme 4" indicates that the precursors coupled to the solid substrate are found to couple together, voiding the reaction that is to create the ring. Accordingly, whether one of Hoger's rings would form in Branton's aperture, or would couple with another of the precursors, adds yet another layer of unpredictability to the combination proposed by the Examiner.

Because the result of the substitution proffered in the rejection is unpredictable, the claimed invention is not obvious. Accordingly, the rejection is improper.

On p. 24 of the Examiner's Answer, the Examiner asserts that the Appeal Brief argues against each reference individually. Appellants respectfully disagree. Arguments such as that Hoger teaches away from the claimed invention necessarily can only be directed at one of the references.

Appellants also respectfully traverse the rejection of claim 1 as being improper, as it would render Branton's invention unsatisfactory for its intended purpose. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Branton's device relies on the molecule passing through an aperture. In the instant case, the Examiner repeatedly relies on the ability of Hoger's molecule to bind with complementary molecules under test. Assuming this was the view of the artisan skilled in the art at the time the present invention was made, then one skilled in the art would not have been motivated to add Hoger's ring to Branton, because doing so would result in the molecule under test binding with the ring and stopping in the aperture, thereby disabling the device. Moreover, because the molecule would be expected to become bound in the aperture, the length of the molecule could not be characterized. Accordingly, one would have expected such a substitution to render Branton's invention unsatisfactory for its intended purpose. Per the rule of *In re Gordon, supra*, such a modification would be improper.

Moreover, the rejection proposed would require an impermissible change in the principle of operation of Branton. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Again, Branton requires that the molecule pass through the aperture. Assuming Hoger's molecule binds with the molecule under test as asserted by the Examiner, the molecule under test would stop in the aperture, thereby disabling Branton's device. Further, Branton relies on a "biological motor" created by polymerase and DNA at p. 36, line 23 to p. 38, line 30. There has been no showing that the ring would create the same "biological motor" effect. Accordingly, the rejection is improper under the rule of *In re Ratti, supra*.

Further, for the reasons presented in the foregoing two paragraphs, one skilled in the art would not have had a reasonable expectation of success, as required by the second prong of the *Graham* test. Therefore, the rejection is improper for this reason as well.

Additionally, throughout the present section of the Examiner's Answer, the Examiner recites that Hoger Scheme 4 shows the macro-cyclic ring couple to a solid support. In the Advisory Action mailed June 24, 2008, the Examiner appeared to agree that Hoger Scheme 4 did not support the previous assertion that Hoger teaches macro-cyclic rings attached to solid

supports in a manner that would meet the claim limitations. Particularly, the Examiner stated in section C of the Advisory Action that "Applicant's citation is directed specifically to solid state reactions of precursors of macrocyclic ring, nor the preformed ring itself. Thus, Applicant's citation has no bearing on the attachment of a preformed ring onto a solid substrate after formation of the ring." (emphasis added) Appellants agree that Hoger Scheme 4 is directed to *synthesis* of the rings on a solid support, not to attachment of preformed rings onto a solid surface. Accordingly, because the Examiner admits that Hoger's Scheme 4 is a synthesis reaction that does not relate to attachment of preformed rings to a solid surface, the rejection improperly relies upon Hoger's Scheme 4 to show attachment of a ring to a solid support. (*See* Office Action mailed April 11, 2008, section 6, 7th paragraph.)

Moreover, Hoger teaches away from coupling rings to a solid support. A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). The Examiner's arguments repeatedly rely on Hoger' Scheme 4 to show macro-cyclic rings attached to solid supports. However, a reading of the column on Hoger p. 2689 directly under the drawing labeled "Scheme 4" indicates that Scheme 4 is not preferred. Particularly, the author notes that the precursors are found to couple together, voiding the reaction that is to create the ring. Further, at one point, the author refers to Scheme 4 as requiring "extreme approaches". *See* Hoger, p. 2689, first column. Accordingly, because Hoger teaches away from a ring coupled to a solid support, the rejection violates the rule of *In re Geisler, supra*, and must be withdrawn.

Issue # 3:

In response to the Examiner's remarks, Appellants hereby incorporate by reference the arguments made in the Appeal Brief.

Issue # 4:

In response to the Examiner's remarks, Appellants hereby incorporate by reference the arguments made in the Appeal Brief.

In view of the remarks set forth hereinabove, all of the independent claims are deemed allowable, along with any claims depending therefrom.

In the event a telephone conversation would expedite the prosecution of this application, the Examiner may reach the undersigned at (408) 971-2573. For payment of any additional fees due in connection with the filing of this paper, the Commissioner is authorized to charge such fees to Deposit Account No. 50-1351 (Order No. LLNLP010).

Respectfully submitted,

By: /Dominic M. Kotab/ Date: February 19, 2009
Dominic M. Kotab
Reg. No. 42,762

Zilka-Kotab, PC
P.O. Box 721120
San Jose, California 95172-1120
Telephone: (408) 971-2573
Facsimile: (408) 971-4660